DEPARTMENT OF HEALTH & HUMAN SERVICES

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Public Health Service

Agency for Toxic Substances
and Disease Registry
Atlanta GA 30333

SEP 27 2000

Ms. Bonita Lavelle
U.S. Environmental Protection Agency
Region VIII
Mail Code 8EPR-SR
999 18th Street
Denver, Colorado 80202

Re: ATSDR Comments on EPA's Baseline Risk Assessment for VBI70 and Swine Study

Dear Ms. Lavelle:

The Agency for Toxic Substances and Disease Registry (ATSDR) appreciates the opportunity to comment on the Environmental Protection Agency's (EPA) baseline risk assessment for the Vasquez Boulevard and I-70 Site (VBI70). ATSDR gathered comments from scientists throughout the agency and have enclosed them in this letter.

Two major issues were identified: 1) the disparity between ATSDR's and EPA's health guidance values, and 2) the dose values used for soil ingestion in pica children. Whereas ATSDR's acute oral MRL for arsenic of 0.005 mg/kg/day and EPA's subacute RfC of 0.05 mg/kg/day are based on the same LOAEL in the same study, the values differ by an order of magnitude because ATSDR incorporated an additional safety factor of 10 to account for the peripheral neuropathy observed at the LOAEL. ATSDR recommends that EPA reevaluate the use of 0.05 mg/kg/day and incorporate the additional safety factor. For the second issue, ATSDR recommends that a value of 5 grams/day be used for soil pica children instead of 2 grams/day to be consistent with EPA's practice and recommendations in EPA's Exposure Factors Handbook.

In addition to the baseline risk assessment, ATSDR is also enclosing comments on the swine bioavailability study conducted specifically for the VBI70 site.

ATSDR apologizes for not meeting EPA's deadline for submitting comments and appreciates EPA's understanding in this matter.

Again, we thank you for the opportunity to comment on the baseline risk assessment and swine study. If you have any questions about ATSDR's comments, please feel free to contact me at (404) 639-0610.

~~Sincerely~~ yours,

Robert C. Williams, P.E., DEE
Assistant Surgeon General
Director, Division of Health Assessment and Consultation

Enclosures
cc:
EPA Working Group Members for the VBI70 Site

ATSDR Comments on EPA's Baseline Risk Assessment for the VBI70 Site
September 26, 2000

1. In Section 2.5 (Selection of Chemicals of Potential Concern), it says that USEPA 1989 (*Risk Assessment Guidance for Superfund*) assumes that any chemical detected at a site is a candidate for selection as a Chemical of Potential Concern (COPC), but identifies a number of methods that may be used for determining when a chemical is not a concern, and may be eliminated from further consideration. Table 2-1 (Data Used to Select COPCs) identifies 23 metals that were detected in the soil samples, and Table 2-2 compares the maximum concentrations of the metals with the soil screening levels. In Section 2.5.2, the reasons for eliminating 21 of the 23 metals for further consideration are explained. The reasons include: 1) eliminating those whose maximum concentrations are below risk-based concentrations based on a risk level of 1E-06 for carcinogens and a Hazard Quotient (HQ) of 1.0 for noncarcinogens; 2) eliminating beneficial minerals; and 3) eliminating chemicals whose risk contributions are minor compared to the risk of others.

   Furthermore, using a HQ of 1.0 as the basis for eliminating a single metal from further consideration does not take into consideration the possible risk of joint toxic action. US EPA recommends calculating total scores, which involves adding the HQs to obtain a Hazard Index (HI). As the HI approaches a value of 1, the concern increases that the mixture will pose a risk. If the HI is greater than 1, the concern is equal to the concern that an individual chemical has exceeded its acceptable level by the same proportion. While this approach assumes dose additivity, it may be used as a first approximation of the risk of joint toxic action. A consideration of whether the joint toxic action of the mixture would be greater than or less than additive could then be made to determine whether the mixture poses a health hazard.

   Based on a preliminary document under development at ATSDR (Draft Interaction Profile for Lead, Arsenic, Cadmium, and Chromium) there is the potential for greater than additive interactions for neurological effects of lead and arsenic. This prediction is based on studies using lead and arsenic concentrations from children's hair as biomarkers of exposure, that have reported a potentiating interaction of lead on arsenic-associated decreases in reading and spelling (Moon et al. 1985); and a potentiating interaction of arsenic on lead-associated maladaptive classroom behavior (Marlow et al. 1985). Although the confidence in this prediction is low (because of limitations in the data and lack of supporting data), the potential for potentiation could be mentioned in this assessment.

2. In the absence of any verified reference values assessing noncarcinogenic risks from less than chronic exposures to arsenic, the EPA used a sub-acute RfD of 0.05 mg/kg/day and a sub-chronic RfD of 0.006 mg/kg/day. We would like to point out that ATSDR has recently derived a provisional acute oral MRL of 0.005 mg/kg/day for inorganic arsenic based on the LOAEL of 0.05 mg/kg/day for facial edema and gastrointestinal symptoms which were characteristic of the initial poisoning as reported by Mizuta et al. (1956).

This report summarized findings from 220 poisoning cases associated with acute arsenic poisoning from consumption of contaminated soy sauce. The acute oral MRL is called provisional because the gastrointestinal effects (nausea, vomiting, diarrhea, and occult blood in feces and gastric and duodenal juice) were considered serious. In addition, serious neurological effects (hypesthesia in legs, abnormal patellar reflex) and cardiological effects (abnormal electrocardiogram) were also observed at the same dose. In deriving the provisional MRL, an uncertainty factor of 10 is applied for the use of a LOAEL. Although it is not customary to base an MRL on a serious LOAEL, due to the significance of the findings, a provisional acute oral MRL of 0.005 mg/kg/day is derived for the purpose of providing health guidance to the public (ATSDR 2000). This MRL is supported by the case study of a husband and wife in upstate New York who experienced gastrointestinal symptoms (nausea, diarrhea, abdominal cramps) which started almost immediately after beginning intermittent consumption of arsenic-tainted drinking water at an estimated dose of 0.05 mg/kg/day (Franzblau and Lilis 1989).

3. EPA's baseline human health risk assessment (BHHRA) (page 36) adopts 0.05 mg/kg/day as the toxicity factor for its subacute RBC, which is designed to access exposure for several days to several weeks. This LOAEL appears to be based on the Mizuta study, a report of arsenic exposure in Japanese eating arsenic-contaminated soy sauce for 2 to 3 weeks. The estimated LOAEL from the Mizuta study is 0.05 mg/kg/day.

It should be noted that at the dose of 0.05 mg/kg/day, the first symptoms appear on day 2 of exposure. Those symptoms include gastrointestinal effects (nausea, vomiting, diarrhea, abdominal cramps) as well as facial edema, fatigue, chillness, headache, sore throat, and nasal discharge.

Since EPA's definition of subacute RBC is for several days to several weeks of continued exposure, more serious symptoms can develop. As mentioned previously, those include decreased sensitivity of the legs to stimulation (hypesthesia), abnormal knee reflex, blood in stools, and abnormal EKG.

In a conversation with EPA staff members on August 28, 2000, they pointed out that the LOAEL of 0.05 mg/kg/day was not an appropriate toxicity factor to use when determining safe levels of exposure to arsenic for short-term exposure and pointed out that a safety factor should be used. This safety factor is particularly important for exposures of 1 to 2 weeks because more serious health effects occur after 1 to 2 weeks of exposure.

ATSDR recommends that EPA reevaluate the use of 0.05 mg/kg/day toxicity factor and incorporate a safety factor to develop a new toxicity factor for calculating the subacute RBC.

4. The subchronic and subacute risk based concentrations (RBC's) developed for the VBI70 site will not protect children.

   The reason that the proposed RBC's do not protect children, particularly the subacute RBC, is that the RBC's do not protect a preschool child who has soil pica one time. EPA's subacute RBC has an exposure frequency of ½, which assumes that a pica child will exhibit pica behavior 1 day out of 2. This assumption doubles the RBC and therefore does not protect soil pica children with a 1-time event.

   In conversations with EPA Region VIII staff and in a fax sent to ATSDR, subchronic and subacute RBC have been shown to be around 1,000 ppm. To show that these RBCs do not protect children, consider the dose to a soil pica child at 950 ppm arsenic in soil. Here is the estimated dose to a soil pica child using EPA's 2,000 mg soil/day and ATSDR's 5,000 soil/day and EPA's suggested RBC of 0.45.

   Dose = C x IR x EF x BF / BW

   Dose = 950 mg/kg x 2,000 mg/day x 1 x 0.45 x E-6 kg/mg / 11 kg = 0.078 mg/kg/day

   Dose = 950 mg/kg x 5,000 mg/day x 1 x 0.45 x E-6 kg/mg / 11 kg = 0.19 mg/kg/day

   Both estimated doses are above the LOAEL (lowest observed adverse effect level) of 0.05 mg/kg/day shown by Mizuta et al and Franzblau and Lillis to cause subjectively reported symptoms of either gastrointestinal effects or facial edema after 1 day of exposure.

   ATSDR recommends that EPA develop an RBC for a 1-time soil pica scenario. Also, see comment # 3 about incorporating a safety factor into the LOAEL of 0.05 mg/kg/day.

5. The exposure scenario of estimating a subchronic dose from 30 days of exposure out of a 120-day exposure is not consistent with the subchronic toxicity factor, which was developed to cover 6 months to 15 years of exposure.

   It may be more protective to use 200 mg/day for longer periods of exposure than to use 500 mg/day for shorter periods of exposure that incorporate an EF of 30/120.

6. The EF for the subchronic RBC assumes 30 days of exposure at 500 mg/day out of 120 days. The risk assessment, however, fails to include the dose that the child receives during the remaining 90 days. A total dose should be calculated.

7. It is unclear what time frame is meant by subchronic exposure period. The BHHRA (page 36) states that the time frame is 6 months to 15 years. The report that Dr. Robert Benson presented to the ATSDR MRL workgroup several months ago states that the time frame for subchronic is 6 months to 10 years. Historically, EPA's chronic RfD applied to 7 to 70 years of exposure leaving subchronic to be time periods less than 7 years.

The choice of these toxicological time frames on one hand is rather arbitrary. For arsenic, one should take into account the current chronic RfD of 0.0003 mg/kg/day or chronic MRL when deciding what time frame to select for a subchronic RfD since no standard definition exists for subchronic.

Because the principle concern at VBI70 for subchronic exposures is children, ATSDR recommends that the time-frame for the subchronic RfD should be 6 months to 18 years so that the subchronic RfD can be used to protect children. A time-frame of 6 months to 10 years would leave out children 11 to 18 years.

8. ATSDR recommends that EPA Region VIII review the selection of 0.05 mg/kg/day as the LOAEL for its subchronic RfD. A review of the literature shows quite a few studies that have LOAELs below 0.05 mg/kg/day for subchronic exposures. Those studies are briefly summarized here. (The reference section at the end of these comments gives the complete citation.)

   A. Mazumder 1998. At 0.009 mg/kg/day for exposures of less than 9 years, Mazumder found an increased prevalence of hyperpigmentation in girls (3.5 cases/100). For exposure periods ranging from 10 to 19 years, Mazumder found an increased prevalence of hyperpigmentation in girls (1.9/100) and boys (3.2/100) and an increased prevalence of keratosis in boys (1.6/100). Mazumber also concluded that malnutrition was not the reason for the high prevalence rates.

   B. Mazumder 1998. The same Mazumder study shows 0.044 mg/kg/day as a second LOAEL for exposures less than 9 years. This LOAEL shows an increased prevalence of keratosis and hyperpigmentation for children less than 9 years. It does not, however, apply to 10-, 11-, 12-, 13-, and up to 18-year-old children. Even if for some reason one discounts the 0.009 mg/kg/day as the lowest LOAEL, the 0.044 mg/kg/day is still lower than the 0.06 mg/kg/day LOAEL EPA used to develop the subchronic RfD and is therefore a more appropriate value. ATSDR still believes, however, that 0.009 mg/kg/day is the lowest LOAEL and is the LOAEL that should be used to develop a subchronic RfD.

   C. Zaldivar 1977a. Zaldivar presents a LOAEL of 0.02 mg/kg/day in 11 to 20 year old children (with a mean age of 19 years.) This LOAEL is supported by a LOAEL of 0.06 mg/kg/day in 0 to 10 year old children (median age is 1.7 years.) What is of note here even though the mean age is 19 years for 0.02 mg/kg/day is the small difference between the dose for the preschool group and the teenagers. The author states that the symptoms were severe in the 0 to 15 year-old-group.

   D. Zaldivar R et al. 1977b. Zaldivar reports on 4 cases of children 2 to 3 years old where the lethal dose over the 2 to 3 years of exposure averages to 0.1 mg/kg/day. This important fact is missed when using 0.05 mg/kg/day as a LOAEL for subchronic exposure. While the author states that malnutrition probably contributed to the increased sensitivity of the Antofagasto population, one of the cases report that the child appeared well nourished.

E. Zaldivar 1980. Zaldivar reports LOAELs of 0.044 mg/kg/day for 5 year olds and 0.02 mg/kg/day for 16 year olds. An appropriate LOAEL for elementary children might be 0.03 mg/kg/day, although the author doesn't give this breakdown but was clearly attuned to estimating age-specific doses for preschool children and older children even though he didn't report every age-specific dose.

F. Chakraborti et al. 1999. Chakraborti doesn't provide a dose estimate but ATSDR estimates a LOAEL of 0.03 mg/kg/day for children less than 12 years based on the following formula for this Indian population:

dose = 0.52 mg/L x 2L/day / 30 kg = 0.346 mg/kg/day.

Some uncertainty exists in this dose estimate because the location is India. It assumes 2 L water consumed each day by a children less than 12 years and an average weight of 30 kg. The author reports that 9% of children were affected.

G. Cebrian 1983. The author doesn't provide a dose but ATSDR estimates a LOAEL of 0.027 mg/kg/day for children less than 9 years based on the following formula for this Mexican population:

dose = 0.4 mg/L x 2 L/day / 30 kg = 0.027 mg/kg/day

The author states that the shortest time to an effect (hypopigmentation) at 0.027 mg/kg/day was 8 years.

It is also possible to estimate a LOAEL for hypopigmentation in adults based on 10 to 19 years of exposure. That LOAEL is 0.02 mg/kg/day based on the following formula:

dose = 0.4 mg/L x 2.5 L/day / 55 kg = 0.02 mg/kg/day for women
dose = 0.4 mg/L x 3.5 L/day / 65 kg = 0.02 mg/kg/day for men

EPA Region VIII may want to present these studies to EPA headquarters in Washington for their consideration in selecting a subchronic RfD for arsenic. There seems to be ample evidence in the literature that 0.05 mg/kg/day is not the lowest LOAEL for subchronic exposures. The lowest LOAEL for subchronic exposures identified so far is 0.009 mg/kg/day.

9. The BHHRA for the VBI70 site (page 35) states that the 200 mg/day used for chronic exposure in children is the upper bound for the average intake across a time interval of 1 year. While this is a standard risk assessment parameter, EPA staff members have stated in VBI70 working group meetings that EPA will protect 95% of the children who live in the VBI70 site. It is unclear how using an average soil intake will protect 95% of the children at the site.

Table 4-23 in EPA's Exposure Factors Handbook states that 200 mg/day may be used as a conservative estimate of the mean but doesn't mention that this value is the 95th

percentile. It seems prudent that if EPA wants to use an upper bound soil intake level for the VBI70 site, that EPA should use a soil intake level that represents the 95th percentile for soil intake.

EPA's Exposure Factors Handbook reports an upper percentile estimate of 400 mg/day for soil and 600 mg/day for soil and dust, although the exact percentile that these numbers represent is not stated. The Handbook states that these soil intakes are estimated from studies of just a few weeks and "are not estimates of usual intake." However, EPA uses the mean soil intakes from these same 2-week studies to estimate soil intake in preschool children for a year. It is unclear why the 200 mg/day estimate, which is based on 2-week studies, can be used for long-term estimates of average soil intake and 400 mg/day, which is based on the same 2-week studies, cannot be used as a long-term intake for an upper percentile group.

The BHHRA states that because of the limitations in the soil intake estimates, the default values used by EPA are on the high side and are an overestimation of actual soil ingestion. It does not seem reasonable to state that the data are limited and then conclude that 200 mg/day is on the high side of actual soil intake for long term exposure.

Table 4-10 in EPA's Exposure Factors Handbook reports the 90th percentile for soil intake over a year to be 1,190 mg/day and a 95th percentile of 1,751 mg/day.

10. The BHHRA assumes that approximately 50% of exposure comes from dust and 50% comes from soil. Please describe the basis for this assumption. In the recommendations section of EPA's Exposure Factor Handbook (page 4-20), the handbook shows a summary of soil ingestion in children (Table 4-22) and reports that the average value for soil ingestion is 146 mg/day and the average value for soil and dust ingestion is 191 mg/day. The percentage intake from soil in this statement is 76.4 while the percentage intake for dust is 23.5. Please explain why EPA Region VIII did not use these percentages for soil and dust.

11. ATSDR suggests that EPA review the Franzblau and Lillis 1989 paper and the Mizuta 1956 paper in more detail. They provide clues to selecting the appropriate LOAEL for acute affects. The Mizuta paper reports that people who consumed arsenic-contaminated soy sauce started experiencing symptoms on day 2 of exposure. The Franzblau and Lillis paper reports on a case study in which a woman reported GI effects the same day as drinking arsenic-contaminated water. The papers provide sufficient information to estimate a 1-time dose that causes adverse health effects. That 1-time dose is 0.05 mg/kg/day.

    The BHHRA (page 36) reports duration of exposure for the Mizuta study as 2 to 3 weeks and for the Franzblau case report as 1 to 2 months. While these facts are true, the exposures did last that long, it is equally important to acknowledge that effects were reported in those exposures the day of or the day after exposure.

The BHHRA states that no reliable studies exists to estimate an acute (single-dose) RfD. Since the Mizuta paper reports on a couple of hundred people and since the paper reports that health effects were observed the day after exposure began, it qualifies as a reliable study for estimating 1-time exposures. ATSDR is in the process of issuing an acute MRL using the Mizuta study. EPA Region VIII should reconsider its position about an acute RfD.

12. Table 4-23 in EPA's Exposure Factors Handbook also cites a range of 5 - 10 grams/day (or 5,000 - 10,000 mg/day) be used for soil pica children and and points out that EPA has used a value of 5 grams for dioxin-contamined sites, a value which is consistent with ATSDR's Public Health Assessment Guidance Manual. In contrast, EPA Region VIII proposes 2 grams/day (or 2,000 mg/day) for soil pica children . The child that had soil pica in the Calabrese study was 2 years old. In conversations with an EPA contractor a year ago, he stated the 2,000 mg/day was EPA Region VIII's estimate for a 1-year-old child and that the lower amount was chosen because the child was 1 year old. ATSDR disagrees with this reasoning.

    In a review of the literature, ATSDR found 2 children in the Calabrese study and 5 children in Wong's study of Jamaican children that report quantitative estimates for soil pica children. The median value for these estimates is 5,000 mg/day. ATSDR recommends that EPA Region VIII use 5,000 mg/day, or that EPA use 10,000 mg/day as recommended in EPA's Exposure Factors Handbook.

13. EPA's use of indoor dust samples in estimating lifetime cancer risk may underestimate exposure and risk for the following reasons:
    A. The one time indoor dust measurement assumes that the same level of contamination will exist in the house for 30 years. This assumption is unreasonable because activity patterns in the house change over the years. For instance, the presence or absence of pets that bring outdoor soil contamination inside is likely to change. The presence or absence of children or the age of children or the presence or absence of gardening activity is likely to change over the years and thus affect the amount of outdoor soil that is brought into house.
    B. The high suction vacuum that was used to collect dust samples from carpets may collect dust from deep in the carpet's pile. Since children are more likely to be exposed to dust on the pile surface rather than dust deep in the pile, the super vac method may be measuring arsenic concentrations that children and adults are not exposed to.
    C. The method of collecting whole house dust sample has not been validated as being the most appropriate method for determining human exposure. For instance, exposure for children occurs in the rooms where the children have the most activity and yet the whole house method collects dust from rooms where the children may have little or not contact. If the arsenic levels are different by area of the house, the whole house measurement will not accurately reflect what children are exposed to.

D. The effect on arsenic concentration when people vacuum their homes is not known. Vacuuming may raise or lower arsenic levels; therefore recent house cleaning using a duster or vacuum cleaner may affect measurements. This is acknowledged by EPA when they ask people not to vacuum their floors before EPA comes in and collects dust samples.

14. EPA uses a lifetime exposure frequency of 30 years out of 70 years. About 13% of people in the VBI70 study live more 30 years in their homes. The range is 14 to 20% in the five neighborhoods. It is reasonable to assume that for those people who live more than 30 years in their home that they are basically lifetime residents of the neighborhood. ATSDR recommends that EPA use an exposure frequency of 70 years to protect these elderly lifetime residents. Studies in arsenic toxicity have shown that the risk of cancer increases with age because of commutative exposure to arsenic; therefore, these elderly people in a sense are more sensitive to arsenic and are more likely to develop cancer from their lifetime exposures.

15. The garden vegetable results presented in Appendix A of the BHHRA may not be reliable. In a conference call with EPA, an EPA official reported that the collected fruit and vegetables were washed in the field. This procedure was not part of the protocol distributed to working group members. This procedure also lacks the controlled conditions of a laboratory for doing a standard wash and may allow soil particles to cling to the outside of the sample, thus artificially raising the detected level. In addition, inter-individual variation in the way different fruits and vegetables are washed in the field may also result in outside contamination of fruit and vegetable with soil particles.

Results from the garden survey support the conclusion that insufficient washing left contaminated soil on the produce. This is apparent in the results for onion, beets, and turnips from property #6, turnips and beets from property #8, and garlic from property #11. In addition, the measurements on these produce did not remove the outer skin which may have had arsenic-containing soil particles adhering to the skin or bound to the skin. In addition, a second garlic sample from the same garden that was collected on a later date showed much lower results. The BHHRA suggests that the lower result in the second garlic sample is an anomaly. ATSDR believes that more careful washing occurred during the second sample collection resulting in lower results. This result makes the entire data set of garden vegetable invalid. Therefore, the garden produce results should not be used to estimate exposure to arsenic in someone's diet.

The BHHRA suggests that soil levels above 50 ppm arsenic are a health hazard for gardening. The data do not seem to support this conclusion for the following reasons:

A. Properties 1, 2, 3, 4, 5, 7, 11, 13, 15, 16, 17, 18, and 19 (or 13 of 19 properties sampled) showed non-detectable or near background levels of arsenic. The arsenic levels in the fruit and vegetables from these background levels are high (for instance, in the range of 0.01 to 0.05 ppm.) Since background levels of arsenic in fruit and vegetables is around 0.001 ppm, the levels reported for the properties mentioned are likely not reliable. ATSDR suspects that this is external contamination from soil particles clinging to the fruit and vegetables.

B. At the recent arsenic conference in San Diego, Dr. Roseanne Lorenzana, an EPA risk assessor from EPA Region X, presented an abstract showing background levels of arsenic in fruit and vegetables. She reported a background level of less than 0.001 ppm.

C. Unfortunately, EPA's detection limit is too high and does not allow EPA to see true background levels of arsenic.

D. Basically, EPA's decision to use 50 ppm as a health hazard is based on one property (property 6.) The number of properties is therefore insufficient to determine an unsafe level for the entire VBI70 site.

E. ATSDR is uncertain whether or not method 6020 is valid for measuring arsenic garden produce.

ATSDR recommends that EPA either resample gardens using a protocol approved by the FDA or give split samples to FDA for confirmation measurements or both. ATSDR also suggests that EPA ask Dr. Rufus Chaney (301-504-8324) with the USDA to review EPA's assessment of arsenic in home-grown produce. Dr. Chaney is a national expert in metal toxicity and assessment.

16. On page 8 of the Data Quality Assessment Phase IIIa Sampling Program, the report is supposed to be summarizing the data quality objectives for the garden produce samples; yet, section 4.1.1 has the same relative percent difference for arsenic and lead as the relative percent difference for dust (see section 3.1.1.) Section 4.2 under accuracy describes the accuracy for dust. It is also suspicious that under 4.2.1, the instrument had the same range of percent recovery as dust (i.e., 97 to 103%). These errors make it suspicious that the proper QA/QC procedures were performed in the lab when it appears that QA/QC procedures from another method were copied into the report.

The comment is unclear under section 4.2.5 (method detection limit study) about the use of a NIST standard. It states that the NIST sample had a SD of < 0.012 for arsenic and lead. In this case, the SD alone cannot be used to determine whether or not the instrument was calibrated correctly and hence was measuring arsenic levels correctly. It also seems odd that the instrument had the same SD for both arsenic and lead. Further reporting from the lab is necessary to verify that the instrument was measuring arsenic correctly.

It is uncertain that the laboratory ran the appropriate matrix spike duplicate. Did the lab use the NIST standard as required periodically (i.e., every 10 samples as reported in section 4) to ensure that the instrument was measuring correctly.

17. Page ES-1, first and second paragraphs - The reader is referred to Figure ES-1, but no Figure ES-1 is present in the draft.

18. Figure ES 2-3. Footnote b. Incomplete statement.

19. Page ES-7, Section 4.2. Noncarcinogenic effects. Change "Oral exposure to high doses of arsenic" to "Acute oral exposure to arsenic". Other symptoms should also be included such as facial edema, gastrointestinal bleeding, abnormal electrocardiogram, and peripheral neuropathy.

20. Page ES-7, Section 4.2 Carcinogenic effects. Suggest revising the last sentence to read: More recent data indicate that chronic oral exposure to arsenic may also increase the risk of internal cancers, including cancer of the bladder, lung, liver, kidney and prostate.

21. Page ES-8. In the EPA derivation of reference dose (RfD) for inorganic arsenic of 0.0003 mg/kg/day, arsenic from the diet was considered as well as arsenic from water. Approximately 5% of the total dose in the Tseng study was attributable to diet.

22. Page ES-9, line 4-5. The statement implies that for EPA the usual level of concern for cancer is 1E-04. What is the reference? The ATSDR level of concern of cancer risk is 1E-6.

23. Page ES-9. Noncancer risks from short-term exposures. What are the exposure durations for "sub-acute" and "sub-chronic" exposures? Is two days for sub-acute and 120 days for sub-chronic? Please clarify.

24. Page ES-10. Risks from home-grown vegetables. How is it that the original high value of the first garlic sample at the 4th property "have been biased high"?

25. Page ES-8 and ES- 10 Typos : "than" not "that".

26. Page ES-11, first full paragraph, last line - delete the second "assumed."

27. Page ES-11. Uncertainty in Exposure Duration. What is the estimated length of time that people live at a particular residence? Seven years?

28. Page ES-11. Uncertainty in Toxicity Factors. It should also be noted that the EPA has recently proposed to lower the drinking water standard for arsenic from 50 ppb to 5 ppb based on the recent analysis of increased risk of internal cancers such as bladder and lung cancers by National Academy of Science.

29. Page ES-12, second paragraph - Change "risks are expressed at..." to "risks are expressed as...."

30. Page ES-12, Section 5.1. It has been ATSDR's position that it is inappropriate to allow children's blood lead levels to exceed the nationally recognized value of 10 ug/dL.

31. Page ES-13, Section 5.3, first paragraph. Accuracy of the contribution of diet to lead exposure is probably not that critical given the fact that dietary levels have been

decreasing over time and its impact to overall lead exposure is probably minimal in comparison to other sources; on the other hand, exposure from hobbies, folk remedies, etc., may be significant. These are difficult to identify without extensive interviewing of the population. The IEUBK cannot take these into account, nor can it take into consideration individual behavior patterns. These are likely to have a greater impact and probably have greater variability than exposure through diet.

32. Page ES-14, Conclusion. Last sentence first paragraph. Replace " is" with "whether" or "if".

33. Page ES-14, last paragraph. As discussed in the previous section 5.3, the two approaches used appear to be at odds. While the difficulties in making assessments are appreciated, what are the bottom-line conclusions in terms of actions? Why is the IEUBK being used exclusively, given the data from the ISE and the (albeit limited) blood lead data.

34. Page 1, first and fourth paragraphs - The reader is referred to Figure 1-1, but no Figure 1-1 is present in the draft.

35. Page 4, last line - Change "hd" to "had."

36. Page 7, Section 2.3.3 Biomonitoring. In the column "As in Urine (ug/L)" the detection frequency is given as 0/15; yet values of 8.7 for the Mean and 10 for the Max are given. How can there be mean and maximum levels of arsenic in the urine if none of the 15 volunteers had arsenic in the urine? Similarly, why do the mean and the maximum levels of arsenic in the hair differ if only 1 individual was found to have a detectable level of arsenic in hair? How many samples/individuals were analyzed?

37. Page 15, Section 2.6.3. The reader is referred to Figure 2-11, but no Figure 2-11 is present in the draft.

38. Page 18. Dermal Contact with Soil. Item 1) in this subsection states that most people do not have extensive and frequent direct contact with soil. Yet, on page 19, it is suggested that uptake of contaminants from soil by homegrown vegetables and fruits may contribute a significant fraction to the total exposure. This implies that at least one member of the families who grow the fruit and vegetables spends a significant amount of time gardening, an activity which certainly involves direct contact with soil.

39. Page 18. Inhalation of Soil/Dust in Air. Although screening level calculations in Appendix B indicate that inhalation of dust particles by residents is a relatively small source of risk compared to incidental ingestion of soil, this doesn't seem to make sense intuitively. Furthermore, Figure 3-1 indicates inhalation of indoor dust is a complete pathway that could be significant.

40. Page 19, last paragraph. The reader is referred to Appendix C for screening levels calculations in workers, but Appendix C shows data only for lead. Where are the calculations for arsenic?

41. Page 26, second paragraph. The sentence "As discussed in Section 2.5.2,..." should be changed to "As discussed in Section 2.6.2,..." The sentence "These data are presented in Figure 2-8" should be changed to "These data are presented in Figure 2-9."

42. Page 29, second paragraph last sentence. Delete "as well as noncancer".

43. Page 29. Noncarcinogenic Effects. The intake of arsenic reported in the Tseng study was "mainly" through the drinking water; it was estimated that 5% of the exposure dose came from diet (rice).

44. Page 30, last line first full paragraph. Suggest revising the last sentence to read: "Chronic oral ingestion of arsenic may also increase the risk of internal cancers, including cancer of the bladder, lung, liver, kidney, and prostate (NRC 1999, ATSDR 2000).

45. Page 29, last full sentence. Suggest replacing "the possibility that sensitive human subgroups may not have been identified" with "to account for some uncertainty in whether the NOAEL of the principle study accounts for all sensitive individuals."

46. Page 31, last paragraph. Change "less well absorbed that..." to "less well absorbed than..."

47. Page 33. The reader is referred to Figure 4-1, but no Figure 4-1 is present in the draft.

48. Page 38, first paragraph, last line - Change the word "that" to "than."

49. Page 40, third paragraph. The ATSDR 1998 reference should be ATSDR 1999 and cited in the reference section as the Toxicological Profile for Lead.

50. Page 41. Change "(see Figure 2-8)" to "(see Figure 2-9)."

51. Page 42. The reader is referred to Figure 5-2, but no Figure 5-2 is present in the draft. The reader is also referred to Figure 2-9, which should be Figure 2-11, but no Figure 2-11 is present in the draft.

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ATSDR's Comments on EPA's Swine Study for the VBI70 Site
September 26, 2000

The Division of Toxicology (DT) and the Division of Health Assessment and Consultation (DHAC) have reviewed the draft document on a study to determine the bioavailability of arsenic from soil at the VBI70 site. The study was performed by scientists at the University of Missouri, Columbia, under the supervision of EPA and ISSI Consulting Group. For the study, soil was sampled from five separate locations, measured for arsenic content, and fed to pigs, in order to measure the resulting excretion factors. The final result is a recommended relative bioavailability (RBA) factor of 0.5 for the VBI70 soils, although this may change based on corrections to the data analysis that have been pointed out during discussion with EPA.

The study has several strong points. Soil was sampled from a number of key areas around the site, and carefully prepared before dosing; and, considerable care was taken in employing analytical controls. In addition, useful information is included, such as arsenic speciation and mass-balance checks.

ATSDR has the following comments and suggestions for the VBI70 swine study.

1. ATSDR recommends that EPA have the swine study for the VBI70 Site peer reviewed by an external panel of scientists who have conducted research in the field.

2. The authors assume that the chronic oral RfD is based upon water studies (page 1, 3rd from last line). It should be noted that in the RfD derivation, arsenic from the diet was considered as well as arsenic from water. Approximately 5 % of the total dose in the Tseng study was attributable to diet.

3. On page 13 of EPA's report Relative Bioavailability of Arsenic in Soils from the VBI70 site (the RBA report), a table shows the slope for the urinary excretion fraction (UEF) and the fecal excretion fraction. ATSDR is concerned that arsenic sequestered in the tissues of the pig will affect the RBA that is calculated and requests that EPA demonstrate that this is not the case.

4. Pentavalent arsenic (As+5) was used as the reference material whereas most of the arsenic in site soil, at least in 3 of the 5 test materials, is trivalent arsenic (As+3). Pentavalent arsenic is likely to have different binding affinities to proteins and other macromolecules than trivalent arsenic. This difference in binding affinities is likely to affect its distribution and excretion in the body and therefore would make pentavalent arsenic unsuitable for using as a reference material to estimate RBA for soils that are predominantly trivalent arsenic.

As supporting evidence for differential distribution based on valence state, Vahter and Norin (Environmental Research 21:446-457, 1980) have shown that the distribution of arsenic in plasma and red cells is dependent on valence. Studies on mice given radiolabelled trivalent and pentavalent arsenic at 0.4 mg/kg showed a red cell/plasma ratio of about 2 in mice given trivalent arsenic and about 1 in mice given pentavalent arsenic. Vahter and Norin show that the distribution of trivalent arsenic is greater in the liver and bile compared to pentavalent arsenic in mice. Specifically, 3 times as much trivalent arsenic was found in the bile compared to pentavalent arsenic. If this is the case with humans (or pigs), it has important implications for the swine study since more arsenic from the soil (this arsenic is predominantly in the trivalent form) will be excreted in the feces via enterohepatic recirculation compared to the reference arsenic (this arsenic is in the pentavalent form.) This difference in bile excretion could affect urinary excretion. The same study also showed that more trivalent arsenic remained in the kidney, liver, brain, skeleton, and skin compared to pentavalent arsenic. Generally, tissue levels of trivalent arsenic are higher compared to pentavalent arsenic.

The distribution of trivalent and pentavalent may be similar, though, at very low doses in rabbits (i.e., 0.0005 mg/kg to 0.05 mg/kg) because both forms are readily methylated (Sabbioni E, et al. In: International Conference., Management and Control of Heavy Metals in the Environment, Sept 1979, 167-170.) Vahter states that low doses of trivalent and pentavalent may be distributed evenly to all tissues because of methylation while higher doses may show differential distribution because of insufficient methylation (Archives of Toxicology 51:65-77, 1982.) One thing that needs to be determined is whether the doses of 50 and 125 ug/kg/day given to pigs in the VBI70 swine study was adequately methylated to allow equal distribution of pentavalent and trivalent arsenic or whether or not methylation was insufficient, which would allow differential distribution.

A thorough review of the literature is needed to confirm whether or not differential distribution of the reference material (pentavalent arsenic) is occurring based on valence and based on dose compared to test soil (predominantly trivalent arsenic.)

Please explain why pentavalent arsenic was used instead of trivalent arsenic.

5. Dosing pigs with a powdered form of arsenate may affect the bioavailability of arsenic since solid forms of arsenic tend to be less bioavailable than arsenic in solution. This may have an affect on the evaluation of arsenic toxicity since not only does dose affect toxicity but also the rate of absorption affects toxicity. Are there components of the swine study that shed light on the rate of arsenic absorption that could be used to access arsenic toxicity, particularly acute toxicity?

6. Does drying and sieving affect the release and hence the absorption of arsenic from test material? A difference would affect the RBA.

7. The table on page 4 of the RBA report shows the relative arsenic mass for site soil test materials. Three test material (TM) samples (TM3, 4, and 5) have 81 to 97% arsenic trioxide, which is trivalent. TM1 has 54% trivalent arsenic and TM2 has 22% trivalent arsenic. The remaining arsenic is mostly lead arsenic oxide (PbAsO.) Unfortunately PbAsO occurs in two forms: the pentavalent lead arsenate [Pb3(AsO4)2] and the trivalent lead arsenite [Pb(As02)2]. What form of lead arsenic oxide occurs in the 5 test materials?

   If distribution is different for trivalent and pentavalent arsenic and if soils at the VBI70 site have varying amounts of the two lead arsenic oxide forms, this may affect the ability of a swine study that uses only 5 test soils to accurately predict RBA for the entire site.

8. One of the reasons that the study lasted 11 days was to allow steady state conditions to be established to reduce the variability in arsenic excretion. Because the study established steady state conditions, it should be possible to measure arsenic absorption indirectly by looking at the fecal excretion fraction and assuming that the remaining arsenic fraction is the absorbed fraction. The later approach shows that 27 to 64.5% of arsenic appeared in the feces (mean = 39.6%). This corresponds to a range of 35.5 to 73% for absorbed arsenic (mean = 60.4%).

   In discussions with EPA staff members, a contractor for EPA stated that it was inappropriate to estimate the absorbed arsenic using the fecal excretion fraction because of the delay in arsenic moving through the gut. ATSDR requests that EPA provide supporting documentation to support this conclusion that this indirect method is not appropriate especially in light that steady state conditions were established.

9. The total fraction of the administered arsenic in urine and feces for sodium arsenate and all test material is reported in a table on page 13 of the RBA report. ATSDR suggests that EPA report the total fraction for TM1 through TM5 so that it is clear what fraction of site soil was recovered in urine and feces.

   The average for the total fraction recovered for site soils (TM1 through TM5) is 61% (range 0.53 to 0.77.) This is the statistic that EPA should compare to other animal studies to show consistency.

10. The authors erroneously state that the total fraction of arsenic recovered was 82% (page 13), when it was substantially lower. This did not affect the conclusion, however.

11. ATSDR suggests that EPA compare the UEF for the reference material (sodium arsenate) to other swine studies using sodium arsenate to determine the consistency of the current study in relation to the reference material UEF. ATSDR was able to locate the UEF for sodium arsenate in a pilot study that EPA conducted for developing the swine model (Casteel s et al., Relative bioavailability of arsenic in mining wastes, Dec 1997, page 24.) That report shows the UEF for sodium arsenate to be 0.176, which is significantly different from the UEF for the reference material in the VBI70 swine study of 0.695.

21. Does spillage from the water supply for the cage into the urine collection pan affect the measurement of arsenic in the urine. If so, how is this uncertainty handled in estimating the RBA.

22. It is unclear whether or not the feces were homogenized prior to collecting the 1 gram sample for arsenic analysis. Not homogenizing the feces might give erroneous results.

23. Please explain in more detail why enterohepatic recirculation does not affect the UEF and resultant RBA.

24. There was an instance of anomalies in the data, although it was appropriately addressed. A group of pigs excreted more arsenic than expected; its dose was found to be too high, and it was removed from analysis (page 11).

25. Some of the arsenic standards consistently had higher concentrations than expected (page 7). These discrepancies may have led to a somewhat higher (i.e., conservative) RBA, but this cannot be said for certain without a more extensive study.